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Patentanmeldung Nr. Patent application No. Demande de brevet n°

04290444.1

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

New process for the synthesis of substituted alpha-aminoindan derivatives

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NEW PROCESS FOR THE SYNTHESIS OF SUBSTITUTED ALPHA-AMINOINDAN DERIVATIVES.

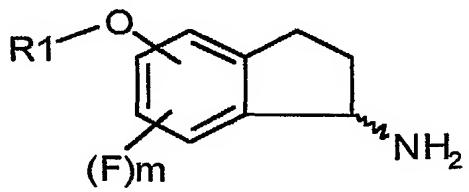
This invention relates to a new process to prepare optically active substituted alpha-amino-indan derivatives useful as synthetic intermediates for the preparation of active pharmaceuticals.

According to the prior art document WO98/27055, optically active substituted alpha-amino-indan derivatives are prepared from an optically active non-substituted alpha-amino-indane with a four steps process in order to obtain optically active alpha-amino-indan substituted compounds. This process involves a Friedel & Craft reaction and a Bayer-Villiger reaction. However, these two reactions show some limitations such as low yields and safety issues.

According to this document optically active substituted alpha-amino-indan derivatives are also prepared from a racemic substituted alpha-amino-indan compounds with an optical resolution process. The limitations of this process are the low yields.

This invention describes a new process for yielding to optically active substituted alpha-amino-indane compounds of general formula (I) hereunder:

(I)



wherein :

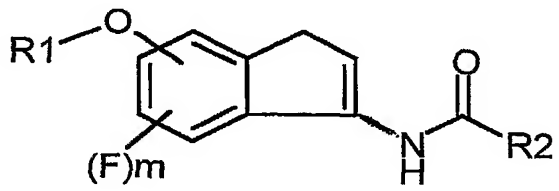
m is an integer equal to 0, 1, 2 or 3,

R_1 is a hydrogen atom, an alkyl group having from 1 to 20 carbon atoms, an aryl group having from 6 to 20 carbon atoms, an alkylaryl group having from 6 to 20 carbon atoms, an alkaloyl group, an aryloyl group, and preferably R1 is an alkyl group having from 1 to 4 carbon atoms,

which comprise :

- an asymmetric hydrogenation reaction of an en-amide derivative of formula (III)

(III)



(R) ou (S)

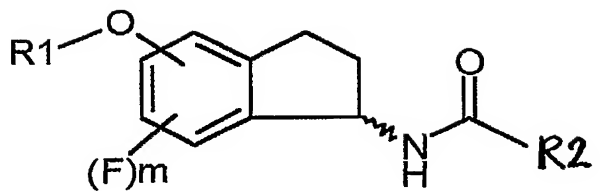
wherein m and R1 are as defined above,

R2 is a hydrogen atom, an alkyl group having from 1 to 20 carbon atoms, an aryl group having from 6 to 20 carbon atoms, an alkylaryl group having from 6 to 20 carbon atoms,

in presence of hydrogen and an optically active catalyst,

in order to obtain an amide derivative of formula (II) :

(II)



(R) ou (S)

- a hydrolysis reaction of the amide derivative of formula (II) obtained in the previous step,

in order to obtain optically active substituted alpha-indanyl amide derivatives of formula (I).

The derivatives of formula (I) can be in a (R) configuration or in a (S) configuration. In the same way, the derivatives of formula (II) can be in a (R) configuration or in a (S) configuration.

In the present application the term alkyl means a straight or branched alkyl group having from 1 to 20 carbon atoms (such as but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl), optionally substituted with a lower alkyl group or a functional group.

The term aryl means an aryl group having from 6 to 20 carbon atoms (such as but not limited to phenyl, tolyl, xylyl, cumenyl, naphthyl), optionally substituted with a lower alkyl group or a functional group, or a fused aryl or a heteroaryl group having from 6 to 20 carbon atoms (such as but not limited to furyl, thienyl, pyrrolyl, imidazolyl, pyridyl, pyrazyl, pyrimidinyl, indolyl, carbazolyl, isoxazolyl, isothiazolyl).

The term alkylaryl means an alkylaryl group having from 6 to 20 carbon atoms (such as but not limited to benzyl, phenethyl, naphthylmethyl) optionally substituted with a lower alkyl group or a functional group.

The term alkaloyl means preferably -COR1 wherein R1 is an alkyl group as defined above (such as but not limited to acetyl, propionyl or pivaloyl).

The term aryloyl means preferably -COR1 wherein R1 is an aryl group as defined above (such as but not limited to benzoyl or phenylacetyl).

The term lower alkyl means a straight or branched alkyl group having from 1 to 8 carbons atoms (such as but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl or tert-butyl).

The term functional group means an halogen, -OH, -OR3, -CN, -COOR3, -COR3, -CONR3R4, -OCOR3, -NH2, -NHR3, -NR3R4, -NHCOR3 and -N(COR3)2, -NO2, -SH, -SR3, wherein R3 and R4 are independently a lower alkyl, an alkylaryl or an aryl group as defined previously. The term halogen means an atom like chlore, brome, fluor or iode.

The optically active catalyst used in the asymmetric hydrogenation of the en-amide derivative of formula (III) is represented by a chiral phosphine transition metal complexe of formula (VII) :

$$M(X)_j(Z)_i(L^*)(Y)_n \qquad (VII)$$

wherein

M is a transition metal selected in the group consisting in ruthenium (Ru), rhodium (Rh) or iridium (Ir)

X is a halogen atom selected in the group consisting in chlore (Cl), brome (Br), fluor (F) or iode (I),

Z is an aryl group having from 6 to 20 carbon atoms or an unsaturated organic group, cyclic or not, selected in the group consisting of olefine, diene or cyano,

L* is a chiral ligand selected in the group consisting of a chiral diphosphine derivative, a chiral atropoisomeric diphosphine derivative, a chiral monodentate phosphoramidine derivative, a chiral biphospholane derivative, a chiral ferrotane derivative or a chiral ferrocenyl phosphine derivative,

Y is an anion such as ClO_4^-, BF_4^-, PF_6^-, SbF_6^-,

j is an integer equal to 0 or 1,

i is an integer equal to 0, 1, 2 or 4,

n is an integer equal to 1 or 2,

The transition metal preferably means ruthenium or rhodium.

The aryl group is a benzene optionally substituted with an alkyl.

The olefine is selected in the group consisting of pi-allyl or 1,3,5,7-cyclooctatetraene and the diene is selected in the group consisting of 1,3-butadiene, 2,5-norbornadiene, 1,5-cyclooctadiene (COD) or cyclopentadiene.

The chiral diphosphine is selected in the group consisting of BICP, DuPHOS, MiniPHOS, BDPMI, TangPHOS, P-PHOS, Tol-P-PHOS or Xyl-P-PHOS.

The chiral atropoisomeric diphosphine is selected in the group consisting of BINAP, TolBINAP, MeOBIPHEP, BINAPO or BINAPO optionally ortho-substituted with an alkyl or an aryl.

The chiral monodentate phosphoramidine is Monophos or Ethylmonophos.

The chiral bisphospholane is selected in the group consisting of Duphos, Me-Duphos or Malphos.

The chiral ferrocenyl phosphine is JOSIPHOS.

The chiral ligand is preferably BINAP or MeOBIPHEP.

The abbreviations listed above have the following meaning :

Concerning the chiral diphosphine derivatives :

BICP : (R,R)-2,2'-bis-diphenylphosphanyl-bicyclopentyl ;

MiniPHOS : 1,3-diphenyl-[1,3]diphospholane ;

BDPMI: 2-Imidazolidinone, 4,5-bis[(diphenylphosphino)methyl]-1,3-dimethyl-, (4S,5S)- ;

TangPHOS : 2,2'-Biphospholane, 1,1'-bis(1,1-dimethylethyl)-, (1S,1'S,2R,2'R) ;

P-PHOS : 3,3'-Bipyridine, 4,4'-bis(diphenylphosphino)-2,2',6,6'-tetramethoxy-, (3S) ; or 3,3'-Bipyridine, 4,4'-bis(diphenylphosphino)-2,2',6,6'-tetramethoxy-, (3R) ;

Tol-P-PHOS : 3,3'-Bipyridine, 4,4'-bis(di-(4-methylphenyl)-phosphino)-2,2',6,6'-tetramethoxy-, (3S) ; or 3,3'-Bipyridine, 4,4'-bis(di-(4-methylphenyl)-phosphino)-2,2',6,6'-tetramethoxy-, (3R) ;

Xyl-P-Phos : 3,3'-Bipyridine, 4,4'-bis(di-(3,5-dimethylphenyl)-phosphino)-2,2',6,6'-tetramethoxy-, (3S) ; or 3,3'-Bipyridine, 4,4'-bis(di-(3,5-dimethylphenyl)-phosphino)-2,2',6,6'-tetramethoxy-, (3R).

Concerning the atropoisomeric chiral diphosphines derivative :

BINAP : (R)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl or (S)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl ;

TolBINAP: (R)-2,2'-Bis(di-p-tolylphosphino)-1,1'-binaphthyl or (S)-2,2'-Bis(di-p-tolylphosphino)-1,1'-binaphthyl ;

MeOBIPHEP: (R)-2,2'-bis-diphenylphosphanyl-6,6'-dimethoxy-biphenyl or (S)-2,2'-bis-diphenylphosphanyl-6,6'-dimethoxy-biphenyl ;

BINAPO : (R)- [1,1'-Binaphthalene]-2,2'-diyl bis(diphenylphosphinite) or (S)- [1,1'-Binaphthalene]-2,2'-diyl bis(diphenylphosphinite) ;

Concerning the chiral monodentate phosphoramidine derivative:

Monophos : Dinaphtho [2,1-d :1',2'-f] [1,3,2]dioxaphosphepin-4-amine, N,N-dimethyl-,(2aR) ;or Dinaphtho [2,1-d :1',2'-f] [1,3,2]dioxaphosphepin-4-amine, N,N-dimethyl-,(11bS).

Concerning the chiral bisphospholane derivative:

Me-Duphos : 1,2-bis-((2R,5R)-2,5-dimethylphospholano)benzene or 1,2-bis-((2S,5S)-2,5-dimethylphospholano)benzene ;

Concerning the chiral ferrocenyl phosphine derivative:

JOSIPHOS : (R)-1-[(S)-2-diphenylphosphino)-ferrocenyl]ethyldicyclohexylphosphine or (S)-1-[(R)-2-diphenylphosphino)-ferrocenyl]ethyldicyclohexylphosphine.

According to a preferred embodiment of the invention, the optically active catalyst of formula (VII) is Ru(COD)(MeOBIPHEP)BF_4^- or Ru(COD)(BINAP)BF_4^-.

The solvant used during the assymetric hydrogenation is an ether such as tetrahydrofuran (THF),

tetrahydropyran or diethyl ether, an aromatic hydrocarbon such as benzene or toluene, a halogenated hydrocarbon such as dichloromethane, an alcohol such as methanol, ethanol or isopropanol. According to a preferred embodiment of the invention the solvant used is the methanol.

The molar ratio of the en-amide derivative of formula (III) to the optically active catalyst (VII) used during the asymmetric hydrogenation is from 100/1 to 10000/1, preferably from 200 to 1000 and is more preferably 500/1.

The hydrogen pressure used during the asymmetric hydrogenation is from 0,5 to 10 bars, preferably from 1 to 8, and more preferably 4.

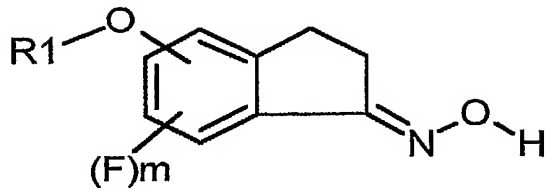
The temperature range used during the asymmetric hydrogenation is from - 20 to 100 °C, preferably from 20 to 100°C, and more preferably 40°C, for a period of time in the range of one hour to three days, preferably 4 hours to 1 day.

The step of the hydrolysis reaction of the amide derivative of formula (II) obtained at the end of the assymetric hydrogenation is performed in presence of an organic acid or a mineral acid such as hydrochloric acid, sulfuric acid or hydrobromic acid, according to methods described in the literature to obtain alpha-aminoindan derivatives of formula (I) in an appropriate solvent.

According to a preferred embodiment of the invention, the en-amide derivative of formula (III) is prepared by the two following step :

- an acylation reaction of an alpha-hydroxyimino-indane derivative of formula (V):

(V)



(R) ou (S)

wherein R_1 and m are as defined above

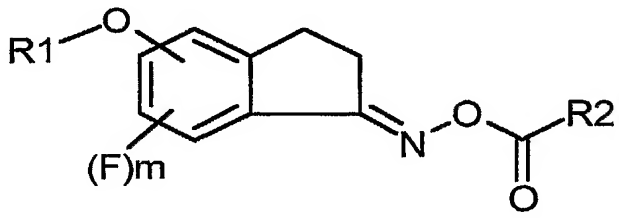
in presence of an organic anhydride of formula (VI) :

$$R_2OC\text{-}O\text{-}COR'_2 \qquad (VI)$$

wherein R_2 and R'_2 identical or different are a hydrogen atom, an alkyl group having from 1 to 20 carbon atoms, an aryl group having from 6 to 20 carbon atoms, an alkylaryl group having from 6 to 20 carbon atoms,

in order to obtain an N-(O-acylimino)-indane derivative of formula (IV) :

(IV)



(R) ou (S)

wherein R_1, m and R_2 are as defined above,

- a hydrogenolyse-acylation reaction of the N-(O-acylimino)-indane derivative of formula (IV) obtained in the previous step,

in presence of an organic anhydride of formula (VI) as defined above and of an heterogeneous catalyst based on a metal transition selected in the group consisting of Pt, Pd, Ir, Rh or Ni,

in order to obtain an en-amide derivative of formula (III).

The molar ratio of the organic anhydride of formula (VI) to the alpha-hydroxyimino-indane derivative of formula (V) used during the acylation reaction is from 1 : 1 to 5 : 1, and is more preferably 1.5 : 1.

The acylation reaction is performed under a temperature range from 0 to 80°C, preferably 20°C, for a period of time in the range of 1 to 8 hours, preferably 2 hours.

The heterogeneous catalyst used during the hydrogenolyse-acylation reaction of the derivative of formula (IV) is selected in the group consisting of PtO_2, Pt/C, Pd/C, $Pd(OH)_2/C$, Ir/C, Rh/C or Raney Ni.

Preferably the heterogeneous catalyst is Ir/C.

The effective amount of the heterogeneous catalyst used during the hydrogenolyse-acylation is in an amount from 0.1% to 30% for 1 mole of the N-(O-acylimino)-indane derivative of formula (IV).

The reaction of hydrogenolyse-acylation is performed with a hydrogen pressure range from 0.5 to 20 bars under a temperature range from -20 to 150°C, preferably 20 to 120°C, for a period of time in the range from 1 to 24 hours.

The molar ratio of the organic anhydride of formula (VI) to the N-(O-acylimino)-indane derivative of formula (IV) used during the hydrogenolyse-acylation reaction is from 1 : 1 to 5 : 1 and preferably 1.5 : 1.

The acylation reaction of the derivative of formula (V) and the hydrogenolyse-acylation reaction of the derivative of formula (IV) are respectively performed in an aprotic non-basic solvent selected in the group consisting of an ether, an organic acid alkyl ester, an aromatic hydrocarbon or a halogenated hydrocarbon.

The ethers are for example tetrahydrofuran (THF) or diethyl ether. The organic acid alkyl ester is but is not limited to ethyl acetate. The aromatic hydrocarbon is but is not limited to toluene. The halogenated hydrocarbon is methylene chloride. The preferred solvent is THF.

The organic anhydride of formula (VI) used during the acylation reaction and the hydrogenolyse-acylation reaction is selected in the group consisting of a dialkyl anhydride, a diaryl anhydride, an alkylarylanhydride, and is preferably an acetic anhydride. The preferred organic anhydride is acetic anhydride.

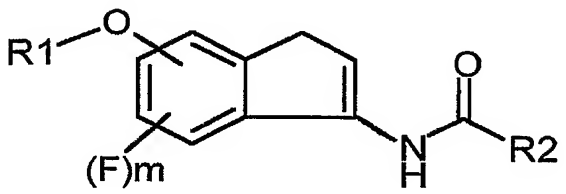
The derivatives of formula (V) (alpha-hydroxyimino-indane) or (IV) (N-(O-acylimino)-indane)) may be used as a syn-form, anti-form or a mixed form of both.

In a preferred embodiment, the two step previously described (the acylation reaction of the derivatives of formula (V) and the hydrogenolyse-acylation reaction of derivatives of formula (IV)) are carried out in one step (also called "one pot" process).

Thus, the derivative of formula (III) is obtained directly from the derivative of formula (V) without isolating specifically the derivayive of formula (IV).

The present invention has also for object the en-amide derivative of formula (III) :

(III)



(R) ou (S)

wherein

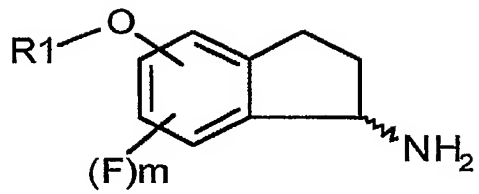
m is an integer equal to 0, 1, 2 or 3,

R_1 is a hydrogen atom, an alkyl group having from 1 to 20 carbon atoms, an aryl group having from 6 to 20 carbon atoms, an alkylaryl group having from 6 to 20 carbon atoms, an alkaloyl group, an aryloyl group, and preferably R1 is an alkyl group having from 1 to 4 carbon atoms,

R_2 is an hydrogen, an alkyl group having from 1 to 20 carbon atoms, an aryl group having from 6 to 20 carbon atoms, an alkylaryl group having from 6 to 20 carbon atoms.

The present invention has also for object the optically active substituted alpha-indanyl amide derivatives of formula (I) :

(I)



wherein

m is an integer equal to 0, 1, 2 or 3,

m is an integer equal to 0, 1, 2 or 3,

R_1 is a hydrogen atom, an alkyl group having from 1 to 20 carbon atoms, an aryl group having from 6 to 20 carbon atoms, an alkylaryl group having from 6 to 20 carbon atoms, an alkaloyl group, an aryloyl group, and preferably R1 and R2 are an alkyl group having from 1 to 4 carbon atoms.

R2 is a hydrogen atom, an alkyl group having from 1 to 20 carbon atoms, an aryl group having from 6 to 20 carbon atoms, an alkylaryl group having from 6 to 20 carbon atoms,

as synthetic intermediates for the preparation of active pharmaceuticals.

The figure 1 is an illustration of the different steps of the new process of the invention for the synthesis of substituted alpha-aminoindan derivatives. The first step of the process relates to acetylation of the corresponding oxime function of the derivatives of formula (V) in the presence of an organic anhydride of formula (VI) in an appropriate solvent to obtain the derivatives of formula (IV).

The second step of the process relates to a hydrogenolyse-acylation of the intermediates of formula (IV) in presence of a heterogeneous catalyst based on a metal transition and an organic anhydride of formula

(VI) in an appropriate solvent to obtain the derivatives of formula (III).

The third step of the process relates to an assymetric hydrogenation reaction of the derivatives of formula (III) in presence of hydrogen and optically active catalyst of formula (VII) and an appropriate solvent to obtain optically active alpha-indanyl amide derivatives of formula (II).

The fourth step is a hydrolysis reaction of derivatives of formula (II) to obtain alpha-amino-indan derivatives of formula (I).

The invention will be better understood from the experimental details described in the following examples which will not limit the scope of the invention in any way.

Example 1

Acetylation reaction : Preparation of Indan-1-on-(O-acetyloxime), methoxy-6 of formula (IV) (in which R1 = R2 = CH_3, m = 0).

6-methoxy-indan-1-one-oxime of formula (V) (in which R_1 = CH_3, m = 0) (30 g, 0.169 mol) is partially dissolved in 180 ml of THF at room temperature. To this solution, acetic anhydride of formula (VI) in which R_2 = R'_2 = CH_3 (47.9 ml, 0.508 mol) is added in 15 minutes at 20°C. The reaction mixture is stirred between 20-30°C during 2 hours and is then concentrated. A colorless liquid is obtained which can solidify. The residue is dissolved in methylene chloride (60 ml). The organic layer is washed with water (60 ml) twice. The organic layer is respectively separated from the aqueous layer, is dried over MgSO4, is filtered off and is concentrated to obtain 56 g of a white solid product (the indan-1-on-(O-acetyloxime), methoxy-6 of formula (IV)). This product is partially dissolved in MTBE (tert-butyl-

methyl ether) (60 ml), is warmed at 55 °C. MTBE (195 ml) is added again slowly to dissolve completely the product. The solution is warmed at reflux temperature during 5 mn. The solution is cooled at room temperature (20 °C) and the solid is filtered off. The solid is dried under vacuum.

28.8 g of white solid (the indan-1-on-(O-acetyloxime), methoxy-6 of formula (IV)) is obtained. The yield is 77%.

Example 2

The preparation of the Acetamide, N-(2,3-dihydro-6-methoxy-1H-inden-1-yl) of formula (III) in which R1 = R2 = CH3, m = 0 .

This example illustrates a "one pot" process from oxime derivative of formula (V) (in which R_1 = CH_3, m = 0).

25 g (0.141 mol) of 6-methoxy-indan-1-one-oxime of formula (V) (in which R_1 = CH_3, m = 0) was dissolved in 190 ml of THF.

The mixture is stirred at room temperature until complete dissolution of the product. Then 40 ml of acetic anhydride of formula (VI) in which R_2 = R'_2 = CH_3 are added drop wise. The reaction mixture is stirred at a temperature between 20-30 °C during 2 hours. 2.5 g of the Ir-carbon (5%) catalyst is added to this reaction mixture. The hydrogenation is carried out at a hydrogen pressure of 7.4 bars at 70-80 °C during 2 hours 15 minutes. After the catalyst Ir/C is filtered off, the filtrate was concentrated to dryness under reduced pressure. The residue is dissolved in 400 ml of toluene and concentrated to dryness under reduced pressure. The residue is dissolved in 75 ml of toluene, the mixture is stirred at a temperature 20°C during 15 mn. The mixture is filtered. The solid is dried under reduced pressure at a temperature of 40-45 °C.

The compound Acetamide, N-(2,3-dihydro-6-methoxy-1H-inden-1-yl)- is obtained with 84 % yield. The chemical purity is 98.4 %.

Example 3

Preparation of N-(6-methoxy-indan-1-yl)-acetamide (R) of formula (II) (in which R_1 = R2 = CH_3 and m = 0.)

The molar ratio of the en-amide derivative of formula (III) to the catalyst (VII) during the asymmetric hydrogenation is 500/1.

3 g (0.0148 mol) of N-(6-methoxy-3H-inden-1-yl)-acetamide of formula (III) (in which R_1 = CH_3 and m = 0) was dissolved in 30 ml of methanol and 24 mg ($2.95\ 10^{-5}$ mol) of (R)-$Ru(OAc)_2$(MeOBIPHEP) of formule (VII) are added . The reaction mixture is flushed with nitrogen (5 times) and is warmed to 40°C. The hydrogenation is carried out with a hydrogen pressure of 8 bars at a temperature of 40 °C during 27 hours.

The reaction mixture is concentrated until complete removal of the methanol.

50 ml of toluene are added to the residue and concentrated to dryness. The operation is repeated with 10 ml and 5 ml of toluene. The solid is dried under vacuum.

The yield is 89 % and the enantiomeric excess (e.e.) is 84.5 %. Then the product is recrystallized in 15 ml of toluene. The yield is 80 % and the enantiomeric excess (e.e.) is > 98 %.

Example 4

Preparation of N-(6-methoxy-indan-1-yl)-acetamide (R) of formula (II) (in which R_1 = CH_3 and m = 0.)

The reaction is carried out in the same manner as in example 3, except that the molar ratio of the en-amide derivative of formula (III) to the catalyst (VII) during the asymmetric hydrogenation is 100/1 and the hydrogenation is carried out at 30°C.
The yield is 95 % and the enantiomeric excess (e.e.) is 86.6 %. Then the product is recrystallized in toluene. The yield is 77 % and the enantiomeric excess is 98,2 %.

Example 5

Preparation of 6-methoxy-indan-1-ylamine (R) of formula (I) (in which R_1 = CH_3 and m = 0.)

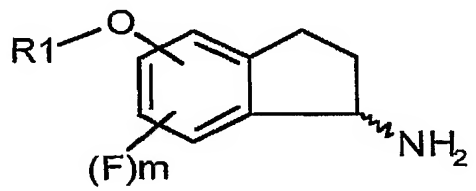
1.5 g of N-(6-methoxy-indan-1-yl)-acetamide (R) of formula (II) (in which R_1 = CH_3 and m = 0) is dissolved in methanol (13 ml). To this methanolic solution of the product a solution of hydrochloric acid 36 % is added (2.2 ml). The mixture is warmed at 90 °C during 8 hours.

After the mixture is cooled down to 25 °C, a solution of hydrochloric acid (1.1 ml) is added again and the mixture is warmed at 90 °C during 7 hours. After the mixture is cooled down to 25 °C, the same operation is repeated with the solution of hydrochloric acid (0.5 ml) and the mixture is warmed at 90 °C during 6 hours. The mixture is concentrated to remove the methanol. Water is added (6.5 ml) to the residue and the mixture is concentrated until the complete removal of methanol. The mixture is warmed at 60 °C and water (7 ml) is added to complete dissolution of the product. Toluene (8 ml) is added to the solution. After removal of the organic layers, the aqueous layer is basified with soda 30 % until a pH range 12 to 13 in presence of xylenes (5 ml) at a temperature 22 °C. The aqueous layer is separated and re-extracted with xylenes (8 ml) 3 times. All organic layers are mixed and concentrated to dryness. The product is obtained with 65 % yield.

CLAIMS.

1. A process for the preparation of optically active substituted alpha-indanyl amide derivatives of formula (I) :

(I)



wherein

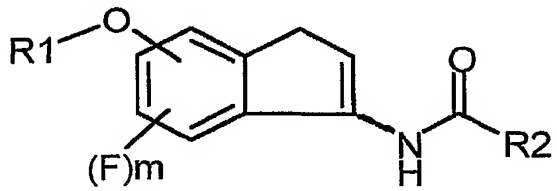
m is an integer equal to 0, 1, 2 or 3,

R_1 is a hydrogen atom, an alkyl group having from 1 to 20 carbon atoms, an aryl group having from 6 to 20 carbon atoms, an alkylaryl group having from 6 to 20 carbon atoms, an alkaloyl group, an aryloyl group, and preferably R1 is an alkyl group having from 1 to 4 carbon atoms,

which comprise :

- an asymmetric hydrogenation reaction of an en-amide derivative of formula (III)

(III)



(R) ou (S)

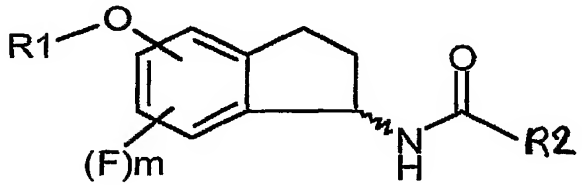
wherein m and R1 are as defined above,

R2 is a hydrogen atom, an alkyl group having from 1 to 20 carbon atoms, an aryl group having from 6 to 20 carbon atoms, an alkylaryl group having from 6 to 20 carbon atoms,

in presence of hydrogen and an optically active catalyst,

in order to obtain an amide derivative of formula (II) :

(II)



(R) ou (S)

- a hydrolysis reaction of the amide derivative of formula (II) obtained in the previous step;

in order to obtain optically active substituted alpha-indanyl amide derivatives of formula (I).

2. Process according to claim 1, wherein the optically active catalyst used in the asymmetric hydrogenation of the en-amide derivative of formula (III) is represented by a chiral phosphine transition metal complexe of formula (VII) :

$$M(X)_j(Z)_i(L^*)(Y)_n \qquad (VII)$$

wherein

M is a transition metal selected in the group consisting of ruthenium (Ru), rhodium (Rh) or iridium (Ir)

X is a halogen atom selected in the group consisting in chlore (Cl), brome (Br), fluor (F) or iode (I),

Z is an aryl group having from 6 to 20 carbon atoms or an unsaturated organic group, cyclic or not, selected in the group consisting of olefine, diene or cyano,

L* is a chiral ligand selected in the group consisting of a chiral diphosphine derivative, a chiral atropoisomeric diphosphine derivative, a chiral monodentate phosphoramidine derivative, a chiral biphospholane derivative, a chiral ferrotane derivative or a chiral ferrocenyl phosphine derivative,

Y is an anion such as ClO_4^-, BF_4^-, PF_6^-, SbF_6^-,

j is an integer equal to 0 or 1,

i is an integer equal to 0, 1, 2 or 4,

n is an integer equal to 1 or 2.

3. The process according to claim 2, wherein the olefine is selected in the group consisting of pi-allyl or 1,3,5,7-cyclooctatetraene and the diene is selected in the group consisting of 1,3-butadiene, 2,5-norbornadiene, 1,5-cyclooctadiene (COD) or cyclopentadiene.

4. The process according to claim 2, wherein the aryl group is a benzene optionally substituted with an alkyl.

5. The process according to claim 2, wherein the chiral diphosphine is selected in the group consisting of BICP, DuPHOS, MiniPHOS, BDPMI, TangPHOS, P-PHOS, Tol-P-PHOS or Xyl-P-PHOS.

6. The process according to claim 2, wherein the chiral atropoisomeric diphosphine is selected in the group consisting of BINAP, TolBINAP, MeOBIPHEP, BINAPO or BINAPO optionally ortho-substituted with an alkyl or an aryl.

7. The process according to claim 2, wherein the chiral monodentate phosphoramidine is Monophos or Ethylmonophos.

8. The process according to claim 2, wherein the chiral bisphospholane is Duphos, Me-Duphos or Malphos.

9. The process according to claim 2, wherein the chiral ferrocenyl phosphine is JOSIPHOS.

10. The process according to any one of claims 1 to 9, wherein the optically active catalyst is $Ru(COD)(MeOBIPHEP)BF_4^-$ or $Ru(COD)(BINAP)BF_4^-$.

11. The process according to any one of claims 1 to 10, wherein the solvant used during the assymetric hydrogenation is selected in the group consisting of an ether, an aromatic hydrocarbon, a halogenated hydrocarbon or an alcohol.

12. The process according to claim 11, wherein the ether is selected in the group consisting of tetrahydrofuran (THF), tetrahydropyran or diethyl ether, the aromatic hydrocarbon is benzene or toluene, the halogenated hydrocarbon is dichloromethane, the alcohol is selected in the group consisting of methanol, ethanol or isopropanol, and is preferably the methanol.

13. The process according to any one of claims 1 to 12, wherein the molar ratio of the en-amide

derivative of formula (III) to the catalyst (VII) used during the asymmetric hydrogenation is from 100/1 to 10000/1, preferably from 200 to 1000 and is more preferably 500/1.

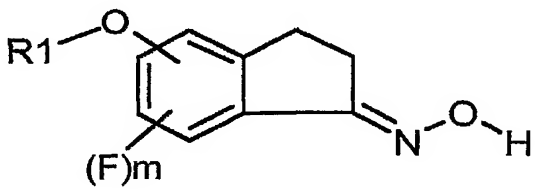
14. The process according to any one of claims 1 to 13, wherein the hydrogen pressure used during the asymmetric hydrogenation is from 0,5 to 10 bars, preferably from 1 to 8, and more preferably 4.

15. The process according to any one of claims 1 to 14, wherein the temperature range used during the asymmetric hydrogenation is from - 20 to 100°C, preferably from 20 to 100°C, and more preferably 40°C.

16. The process according to any one of claims 1 to 15, wherein the en-amide derivative of formula (III) is prepared by the two following step :

- an acylation reaction of an alpha-hydroxyimino-indane derivative of formula (V):

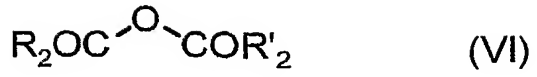
(V)



(R) ou (S)

wherein R_1 and m are as defined above

in presence of an organic anhydride of formula (VI) :

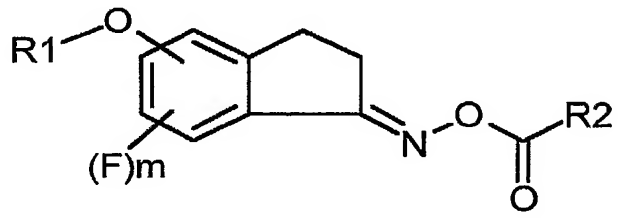


(VI)

wherein R2 and R'2 identical or different are a hydrogen atom, an alkyl group having from 1 to 20 carbon atoms, an aryl group having from 6 to 20 carbon atoms, an alkylaryl group having from 6 to 20 carbon atoms,

in order to obtain an N-(O-acylimino)-indane derivative of formula (IV) :

(IV)



(R) ou (S)

wherein R_1, m and R_2 are as defined above,

- a hydrogenolyse-acylation reaction of the N-(O-acylimino)-indane derivative of formula (IV) obtained in the previous step,

in presence of an organic anhydride of formula (VI) as defined above and of an heterogeneous catalyst based on a metal transition selected in the group consisting of Pt, Pd, Ir, Rh or Ni,

in order to obtain an en-amide derivative of formula (III).

17. The process according to claim 16, wherein the molar ratio of the organic anhydride of formula (VI) to the alpha-hydroxyimino-indane

derivative of formula (V) used during the acylation reaction is from 1 : 1 to 5 : 1 and preferably 1.5 : 1.

18. The process according to claim 16 or 17, wherein the heterogeneous catalyst used during the hydrogenolyse-acylation reaction of the derivative of formula (IV) is selected in the group consisting of PtO_2, Pt/C, Pd/C, $Pd(OH)_2/C$, Ir/C, Rh/C or Raney Ni, and is preferably Ir/C.

19. The process according to any one of claims 16 to 18, wherein the effective amount of the heterogeneous catalyst used during the hydrogenolyse-acylation is in an amount from 0.1% to 30% for 1 mole of the N-(O-acylimino)-indane derivative of formula (IV).

20. The process according to any one of claims 16 to 19, wherein the molar ratio of the organic anhydride of formula (VI) to the N-(O-acylimino)-indane derivative of formula (IV) used during the hydrogenolyse-acylation reaction is from 1 : 1 to 5 : 1 and preferably 1.5 : 1.

21. The process according to any one of claims 16 to 20, wherein the acylation reaction of the derivative of formula (V) and the hydrogenolyse-acylation reaction of the derivative of formula (IV) are respectively performed in an aprotic non-basic solvent selected in the group consisting of an ether, an organic acid alkyl ester, an aromatic hydrocarbon or a halogenated hydrocarbon.

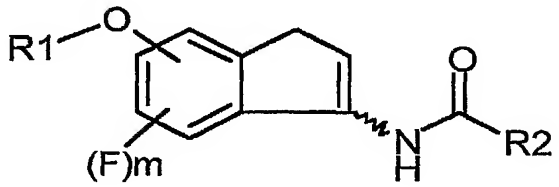
22. The process according to any one of claims 16 to 21, wherein the organic anhydride of formula (VI) used during the acylation reaction and the hydrogenolyse-acylation reaction is selected in the group consisting of a dialkyl anhydride, a diaryl

anhydride or an alkylarylanhydride, and is preferably an acetic anhydride.

23. The process according to any one of claims 16 to 22, wherein the derivative of formula (III) is obtained directly from the derivative of formula (V) without isolating specifically the derivative of formula (IV).

24. En-amide derivative of formula (III) :

(III)



(R) ou (S)

wherein

m is an integer equal to 0, 1, 2 or 3,

R_1 is a hydrogen, an alkyl group having from 1 to 20 carbon atoms, an aryl group having from 6 to 20 carbon atoms, an alkylaryl group having from 6 to 20 carbon atoms, an alkaloyl group or an aryloyl group,

R2 is a hydrogen atom, an alkyl group having from 1 to 20 carbon atoms, an aryl group having from 6 to 20 carbon atoms, an alkylaryl group having from 6 to 20 carbon atoms.

ABSTRACT

A process for the preparation of optically active substituted alpha-indanyl amide derivatives of formula (I), which comprise :

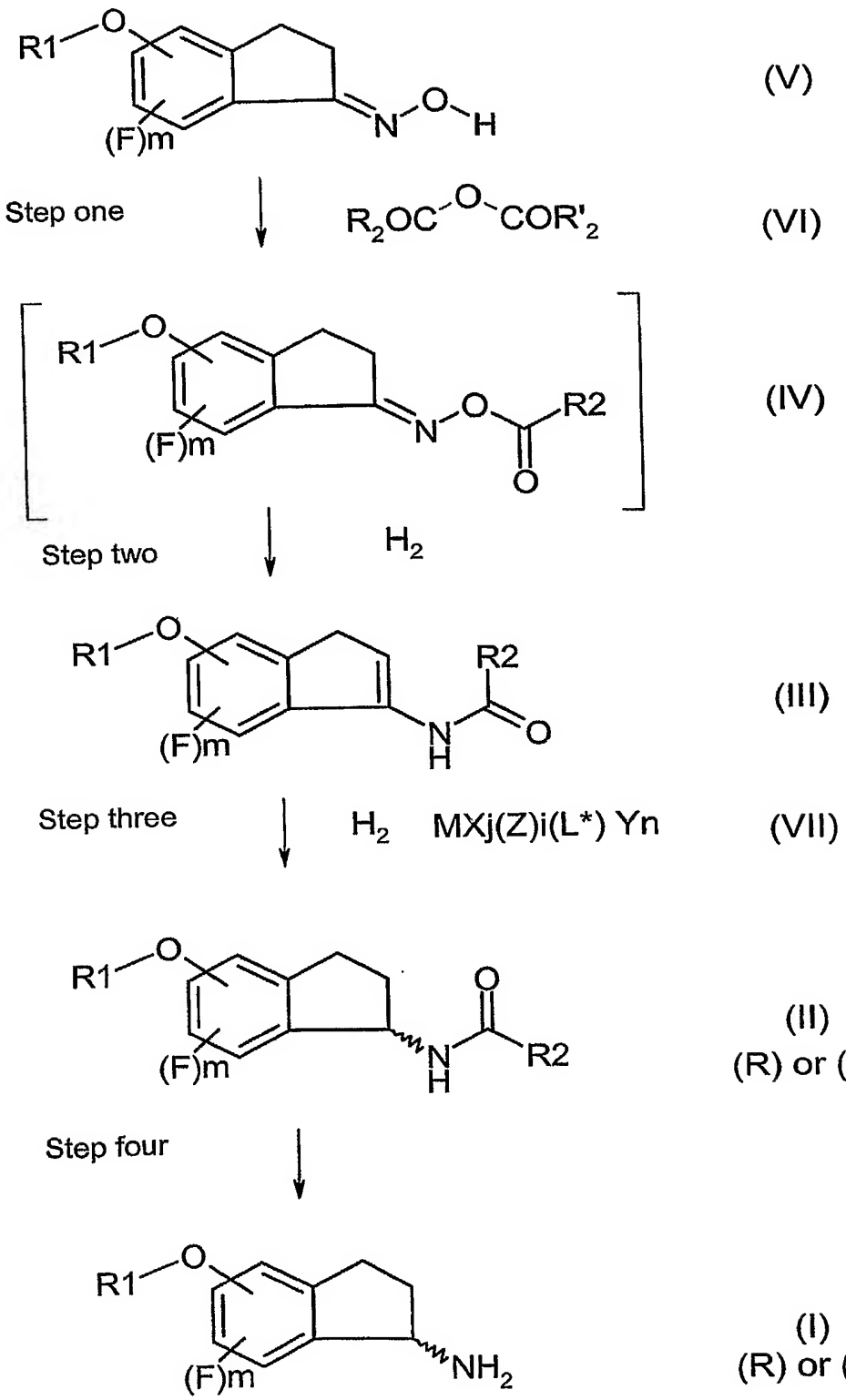
- an asymmetric hydrogenation reaction of an en-amide derivative of formula (III) in presence of hydrogen and an optically active catalyst,

in order to obtain an amide derivative of formula (II),

- a hydrolysis reaction of the amide derivative of formula (II) obtained in the previous step,

in order to obtain optically active substituted alpha-indanyl amide derivatives of formula (I).

Figure 1


R1
O
(F)m
N
O
H
(V)
Step one
R2OC
O
COR'2
(VI)
R1
O
(F)m
N
O
R2
O
(IV)
Step two
H2
R1
O
(F)m
R2
N
H
O
(III)
Step three
H2
MXj(Z)i(L*) Yn
(VII)
R1
O
(F)m
O
N
H
R2
(II)
(R) or (S)
Step four
R1
O
(F)m
NH2
(I)
(R) or (S)